

METHODS OF TREATING SKIN DISORDERS USING THIO-OXINDOLE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATION

5 This is a non-provisional of US Patent Application No. 60/391,913, filed June 25, 2002.

BACKGROUND OF THE INVENTION

10 This invention relates to the treatment of skin disorders, including acne and hirsutism, and for conditioning the skin using compositions containing small molecules.

 In view of the vast number of skin disorders diagnosed to date, a large amount of research has been conducted regarding the treatment of such disorders. Although many skin disorders are not considered dangerous, if left untreated irreversible
15 physical scarring can result.

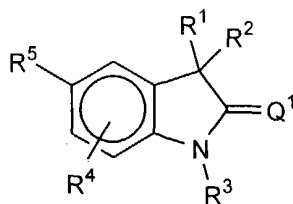
 There are a number of treatments known to alleviate the symptoms of skin disorders, and include oral, intravenous, and topical delivery of compositions containing active agents, as well as surgical procedures such as laser therapy. However, such treatments may result in unpleasant side effects, tend to be suppressive
20 rather than curative, are costly, and/or tend to worsen the disorder.

 There exists a continued need in the art for alternative methods of alleviating the symptoms and/or resolving skin disorders and for conditioning the skin.

SUMMARY OF THE INVENTION

25 In one aspect, the invention provides methods of treating skin disorders including the step of delivering to a mammal a composition containing a compound of formula I, or tautomers thereof, and a physiologically compatible carrier, wherein

formula I is:



I

In a further aspect, the invention provides a method of treating acne including the step of delivering to a mammal a composition containing a compound of formula

5 I.

In another aspect, the invention provides a method of treating hirsutism including the step of delivering to a mammal a composition containing a compound of formula I.

10 In yet a further aspect, the invention provides a method for conditioning the skin of a mammal, which includes the step of delivering to a mammal a composition containing a compound of formula I.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

15 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods of treating skin disorders including delivering to a mammal a composition comprising a compound of formula I in a regimen.

20 Preferably, the mammalian patient treated according to the present invention is a human, and more preferably a female.

The term "tautomer" is meant to describe a compound which can exist in more than one isomeric state.

The term "skin" is meant to describe the outer covering of a mammalian form including, without limitation, the epidermis, dermis, and subcutaneous tissues.

Typically, the skin can include other components such as hair follicles and sweat glands.

The term "acne" is meant to include any skin disorder where a skin pore becomes blocked and/or thereby becomes inflamed. The term acne includes without
5 limitation superficial acne, including comedones, inflamed papules, superficial cysts, and pustules; and deep acne, including deep inflamed modules and pus-filled cysts. Specific acne conditions can include, but are not limited to, acne vulgaris, acne comedo, papular acne, premenstrual acne, preadolescent acne, acne venenata, acne cosmetica, pomade acne, acne detergentica, acne excoricee, gram negative acne, acne
10 rosacea, pseudofolliculitis barbae, folliculitis, perioral dermatitis, and hidradenitis suppurativa.

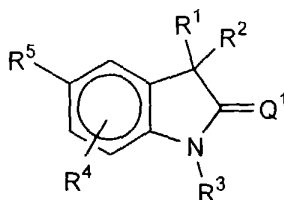
The term "hirsutism" is meant to describe a skin disorder where an overgrowth of hair growth is observed in areas of the body which are not normally subject to excessive hair growth.

15 A number of skin disorders can be treated according to the methods of the present invention and include skin disorders of the hair follicles and sebaceous glands. Preferably, skin disorders such as acne and hirsutism, among others, can be treated according to the present invention.

20 Other skin disorders can include dry/chapped skin, seboria, psoriasis, or alopecia. The invention is also useful for treating the skin against the effects of environmental conditions.

I. Compounds Useful in the Methods of the Invention

25 In one embodiment, the methods of the present invention include the delivery of compounds of the formula I, the preparation of which is described in US Patent No. 6,355,648 and International Patent Publication No. WO 00/66555, and hereby incorporated by reference. The compounds of formula I have the structure:



I

wherein:

R¹ and R² are selected from the group consisting of H, alkyl, substituted alkyl,
 5 OH, O(alkyl), O(substituted alkyl), O(Acetyl), aryl, substituted aryl, heterocyclic ring,
 substituted heterocyclic ring, alkylaryl, substituted alkylaryl, alkylheteroaryl,
 substituted alkylheteroaryl, 1-propynyl, substituted 1-propynyl, 3-propynyl, and
 substituted 3-propynyl;

or R¹ and R² are joined to form a ring selected from the group consisting of
 10 -CH₂(CH₂)_nCH₂-, -CH₂CH₂C(CH₃)₂CH₂CH₂-, -O(CH₂)_mCH₂-, -O(CH₂)_pO-,
 -CH₂CH₂OCH₂CH₂-, -CH₂CH₂N(H)CH₂CH₂-, and -CH₂CH₂N(alkyl)CH₂CH₂-;

m is an integer from 1 to 4;

n is an integer from 1 to 5;

p is an integer from 1 to 4;

15 or R¹ and R² form a double bond to C(CH₃)₂, C(cycloalkyl), O, or
 C(cycloether);

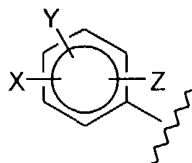
R³ is selected from the group consisting of H, OH, NH₂, C₁ to C₆ alkyl,
 substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₃ to C₆ alkenyl, alkynyl,
 substituted alkynyl, and COR^A;

20 R^A is selected from the group consisting of H, C₁ to C₃ alkyl, substituted C₁ to
 C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, and
 substituted C₁ to C₃ aminoalkyl;

R⁴ is selected from the group consisting of H, halogen, CN, NH₂, C₁ to C₆
 alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆
 25 aminoalkyl, and substituted C₁ to C₆ aminoalkyl;

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring having the structure:



X is selected from the group consisting of halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, $S(O)$ alkyl, $S(O)_2$ alkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, substituted C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring comprising 1 to 3 heteroatoms, $CONH_2$, $CSNH_2$, $CNHNHOH$, CNH_2NOH , $CNHNHOH$, COR^B , CSR^B , $OCOR^B$, and $NR^C COR^B$;

R^B is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 thioalkyl, and substituted C_1 to C_3 thioalkyl;

b) a five or six membered heterocyclic ring comprising 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and having one or two independent substituents from the group consisting of H, halogen, CN, NO_2 , C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, COR^D , CSR^D , and $NR^E COR^D$;

R^D is H, NH_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^6 is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or C_1 to C_4CO_2 alkyl;

or

- c) an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, wherein said moiety is optionally substituted by from 1 to 3 substituents selected from the group consisting of halogen, alkyl, substituted alkyl, CN, NO_2 , alkoxy, substituted alkoxy, and CF_3 ;

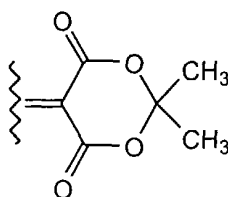
Q^1 is S, NR^7 , or CR^8R^9 ;

- R^7 is selected from the group consisting of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, SO_2CF_3 , OR^{11} , and $NR^{11}R^{12}$;

- R^8 and R^9 are independent substituents selected from the group consisting of H, alkyl, substituted alkyl, acyl, substituted acyl, aroyl, substituted aroyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, NO_2 , CN, and CO_2R^{10} ;

R^{10} is C_1 to C_3 alkyl or substituted C_1 to C_3 alkyl;

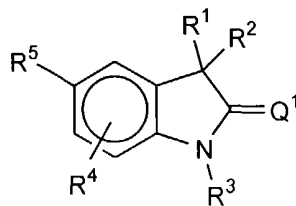
or CR^8R^9 comprise a six membered ring having the structure:



- R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl; or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

In some embodiments, R^8 and R^9 are selected from among substituted or unsubstituted C_1 - C_6 alkyls.

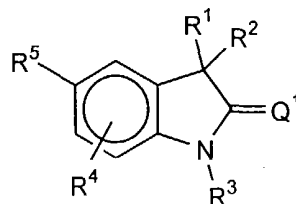
- In one embodiment, in the compound of formula I:



I

- R^1 and R^2 are alkyl or substituted alkyl; R^3 is H; R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl; the other substituents are as defined above, and a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

In another embodiment, in compound of formula I:



I

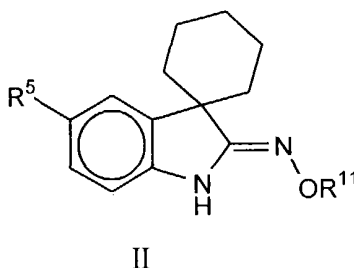
- R^1 and R^2 are joined to form a ring selected from the group consisting of $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_m\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{N}(\text{alkyl})\text{CH}_2\text{CH}_2-$. In some embodiments, the ring has the structure



- In one embodiment of the compound of formula I, when R^1 and R^2 are joined to form a ring, R^3 is H; R^8 and R^9 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, NO_2 , CN, and CO_2R^{10} ; and the other substituents are as defined above; or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

In a further embodiment, in the compound of formula I, R^3 is H; Q^1 is S or NR^7 ; R^7 is selected from the group consisting of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, SO_2CF_3 , OR^{11} , and $NR^{11}R^{12}$; R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl; or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

10 In a further embodiment the compound is of formula II:

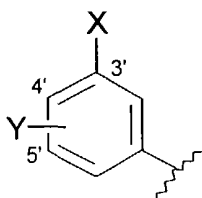


wherein:

R^{11} is selected from the group consisting of H, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl;

15 R^5 is (i), (ii), or (iii):

(i) a substituted benzene ring having the structure:

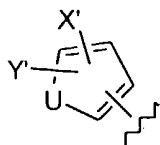


wherein:

20 X is selected from the group consisting of halogen, CN, $CONH_2$, $CSNH_2$, $CONHalkyl$, $CSNHalkyl$, $CON(alkyl)_2$, $CSN(alkyl)_2$, $CNHNHOH$, CNH_2NOH , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring comprising 1 to 3 heteroatoms, and C_1 to C_3 thioalkyl;

Y is selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, and C₁ to C₃ thioalkyl;

(ii) a five membered ring having the structure:



5 wherein:

U is O, S, or NR⁶;

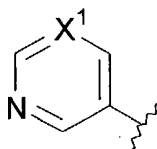
R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group consisting of halogen, CN, NO₂, CONH₂, CNHNHOH, CNH₂NOH, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂,

10 CSN(alkyl)₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H, F, and C₁ to C₄ alkyl; or

(iii) a six membered ring having the structure:



wherein:

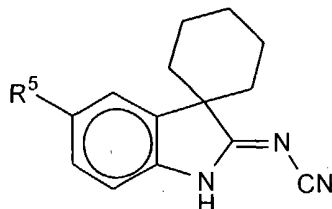
15 X¹ is N or CX²;

X² is halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂ or NO₂;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R⁵ is the five membered ring (ii) and U is O or S.

20 In yet another embodiment, the compound is of formula III:

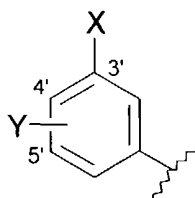


III

wherein:

R^5 is (i), (ii), or (iii):

(i) a substituted benzene ring having the structure:

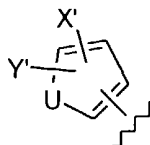


5 wherein:

X is selected from the group consisting of halogen, CN, CONH_2 , CSNH_2 , CONHalkyl , CSNHalkyl , CON(alkyl)_2 , CSN(alkyl)_2 , CNHNOH , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring comprising 1 to 3 heteroatoms, and C_1 to C_3 thioalkyl;

10 Y is selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, and C_1 to C_3 thioalkyl;

(ii) a five membered ring having the structure:



wherein:

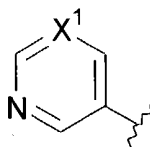
15 U is O, S, or NR^6 ;

R^6 is H, C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl ;

X' is selected from the group consisting of halogen, CN, NO_2 , CONH_2 , CSNH_2 , CONHalkyl , CSNHalkyl , CON(alkyl)_2 , CSN(alkyl)_2 , C_1 to C_3 alkyl, and C_1 to C_3 alkoxy;

20 Y' is selected from the group consisting of H, F and C_1 to C_4 alkyl; or

(iii) a six membered ring having the structure:



wherein:

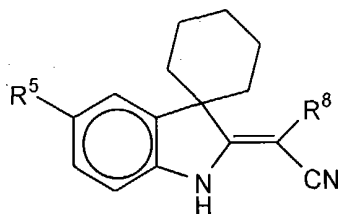
X^1 is N or CX^2 ;

X^2 is halogen, CN, $CONH_2$, $CSNH_2$, $CONHalkyl$, $CSNHalkyl$, $CON(alkyl)_2$, $CSN(alkyl)_2$ or NO_2 ;

5 or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R^5 is the five membered ring (ii) and U is O or S.

In a further embodiment, the compound is of formula IV:



IV

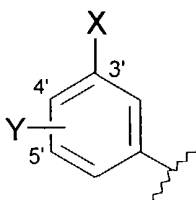
wherein:

10 R^8 is selected from the group consisting of H, CO_2R^{10} , acyl, substituted acyl, aroyl, substituted aroyl, alkyl, substituted alkyl, and CN;

R^{10} is C_1 to C_3 alkyl;

R^5 is (i), (ii), or (iii):

(i) a substituted benzene ring having the structure:



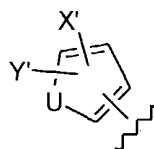
15

wherein:

X is selected from the group consisting of halogen, CN, $CONH_2$, $CSNH_2$, $CONHalkyl$, $CSNHalkyl$, $CON(alkyl)_2$, $CSN(alkyl)_2$, $CNHNOH$, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring
20 comprising 1 to 3 heteroatoms, and C_1 to C_3 thioalkyl;

Y is selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, and C_1 to C_3 thioalkyl;

(ii) a five membered ring having the structure:



wherein:

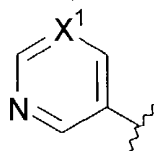
U is O, S, or NR⁶;

5 R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group consisting of halogen, CN, NO₂, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H, F and C₁ to C₄ alkyl;

10 (iii) a six membered ring having the structure:



wherein:

X¹ is N or CX²;

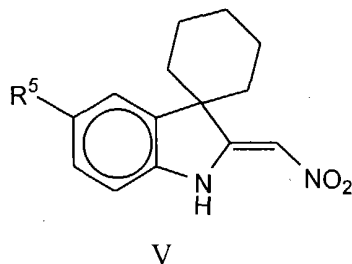
X² is halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl,

15 CON(alkyl)₂, CSN(alkyl)₂ or NO₂;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R⁵ is the five-membered ring (ii) and U is O or S.

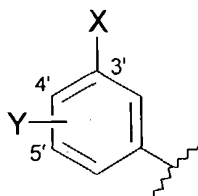
In another embodiment, the compound is of formula V:



V

20 R⁵ is (i), (ii), or (iii):

(i) a substituted benzene ring having the structure:

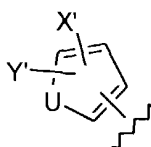


wherein:

X is selected from the group consisting of halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂, CNHNOH, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring comprising 1 to 3 heteroatoms, and C₁ to C₃ thioalkyl;

Y is selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, and C₁ to C₃ thioalkyl;

(ii) a five membered ring having the structure:



10

wherein:

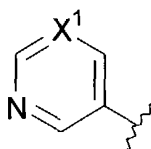
U is O, S, or NR⁶;

R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group consisting of halogen, CN, NO₂, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H, F, and C₁ to C₄ alkyl;

(iii) a six membered ring having the structure:



20

wherein:

X¹ is N or CX²;

X² is halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl,

CON(alkyl)₂, CSN(alkyl)₂ or NO₂;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R⁵ is the five membered ring (ii) and U is O or S.

In yet another embodiment, the compound is 5'-(3-

- 5 Chlorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-thione, 3-(1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)benzonitrile, 4-1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2-thiophenecarbonitrile, 3-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile, 4-Methyl-5-(1,2-dihydro-2-thioxospiro[cyclohexane-1,3-[3H]-indol]-5-yl)-2-
- 10 thiophenethioamide, 5-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5'-yl)-1H-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-(tert-butoxycarbonyl)-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-H-pyrrole-2-carbonitrile, 5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-pyrrole-2-carbonitrile, 5-
- 15 (1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-3-thiophenecarbonitrile, 5-(1,2-Dihydro-thioxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-2-thiophenecarbonitrile, 5-(3-Fluoro-4-methoxyphenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(2-Amino-5-pyrimidinyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 3-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-
- 20 5-yl)-5-fluorobenzonitrile, 5-(3-chlorophenyl)-3,3-dimethyl-1,3-dihydro-2H-indole-2-thione, 3-Benzyl-5-(3-chlorophenyl)-3-methyl-1,3-dihydro-2H-indole-2-thione, 4-(3,3-dimethyl-2-thioxo-2,3-dihydro-1H-indol-5-yl)-2-furonitrile, 5-(3-methoxyphenyl)-3,3-dimethyl-1,3-dihydro-2H-indole-2-thione, 3-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-fluorobenzonitrile, 5-(1,2-Dihydro-2-
- 25 thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-3-pyridinecarbonitrile, 5-(3,4-Difluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(5-Chloro-2-thienyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-3-furancarbonitrile, 5-(3-Chloro-4-fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(3-Chloro-5-

- fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(3,5-Difluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-propyl-2-thiophenecarbonitrile, 5-(3-Fluoro-4-nitrophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 4-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-furancarbonitrile, 5''-(3-Chlorophenyl)spiro[cyclobutane-1,3''-[3H]indol]-2''(1''H)-thione, 5''-(2-Chlorophenyl)spiro[cyclohexane-1,3''-[3H]indol]-2''(1''H)-thione, 5''-(4-Chlorophenyl)spiro[cyclohexane-1,3''-[3H]indol]-2''(1''H)-thione, 5-(1'',2''-Dihydro-2''-thioxospiro[cyclohexane-1,3''-[3H]indol]-5''-yl)-4-methyl-2-thiophenecarbonitrile, 5-(1'',2''-Dihydro-2''-thioxospiro[cyclohexane-1,3''-[3H]indol]-5''-yl)-2-thiophenecarbonitrile, 5''-(3-Fluorophenyl)spiro[cyclohexane-1,3''-[3H]indol]-2''(1''H)-thione, 5-(3-Hydroxyphenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(3-chlorophenyl)-3,3-diethyl-1,3-dihydro-2H-indole-2-thione, 5-(4-Fluoro-3-(trifluoromethyl)phenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 4-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-fluorobenzonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-n-butyl-2-thiophenecarbonitrile, 5-(3-Fluoro-5-methoxyphenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-thione, 5-(3-Chlorophenyl)-N-hydroxyspiro[cyclohexane-1,3'-[3H]indol]-2-amine, N-(Acetyloxy)-5'-(3-chlorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2''amine, 5'-(3-Fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(2-Fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(4-Fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(3,4-difluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(3-methoxyphenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(3-nitrophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 5'-(3-cyanophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one oxime, 3-(1',2'-Dihydro-2'-(hydroxyimino)spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile, 5-(Spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-4-methyl-2-thiophenecarbonitrile, 5-(Spiro[cyclohexane-1,3'-[3H]indol]-2'-

(hydroxyimino)-5'-yl)-2-thiophenecarbonitrile, 4-(Spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-2-thiophenecarbonitrile, 5-(Spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-1H-pyrrole-1-methyl-2-carbonitrile, 5-(spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-1H-pyrrole-2-carbonitrile, 4-(Spiro[cyclohexane-1,3'-[3H]indol]-2'(acetoxymino)-5'-yl)-2-thiophenecarbonitrile, 3-Fluoro-N'-hydroxy-5-(2'-(hydroxyamino)spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)benzenecarboximidamide, N'-Hydroxy-5-(spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-4-methyl-2-thiophenecarboximidamide, N'-Hydroxy-4-(spiro[cyclohexane-1,3'-[3H]indol]-2'-hydroxyimino)-5'-yl-2-thiophenecarboximidamide, N'-Hydroxy-5-(spiro[cyclohexane-1,3'-[3H]indol]-2'-(hydroxyimino)-5'-yl)-2-thiophenecarboximidamide, 5'-(3-Chlorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 5'-(3-Cyano-5-fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 5'-(5-Cyano-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 5'-(5-Cyano-thiophen-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 5'-(5-Cyano-3-methyl-thiophen-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 5'-(5-Cyano-thiophen-3-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, 3-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile, 5-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1H-pyrrole-2-carbonitrile, 5-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-1H-pyrrole-2-carbonitrile, 5-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-2-carbonitrile, 5-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-4-methyl-thiophene-2-carbonitrile, 4-(2'-Cyanomethylene-spiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-2-carbonitrile, or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof. Preferably, the compound is 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide, or a tautomer or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

The compounds utilized according to the present invention can contain one or more asymmetric centers and can thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry, the compounds can include optical isomers and diastereomers; racemic and resolved enantiomerically pure R and S stereoisomers; other mixtures of the R and S stereoisomers; and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having about 1 to about 8 carbon atoms, and preferably about 1 to about 6 carbon atoms. The term "alkenyl" is used herein to refer to both straight- and branched-chain alkyl groups having one or more carbon-carbon double bonds and containing about 2 to about 8 carbon atoms. Preferably, the term alkenyl refers to an alkyl group having 1 or 2 carbon-carbon double bonds and having 2 to about 6 carbon atoms. The term "alkynyl" is used herein to refer to both straight- and branched-chain alkyl groups having one or more carbon-carbon triple bond and having 2 to about 8 carbon atoms. Preferably, the term alkynyl refers to an alkyl group having 1 or 2 carbon-carbon triple bonds and having 2 to about 6 carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl groups, respectively, having one or more substituents including, without limitation, halogen, CN, OH, NO₂, amino, aryl, heterocyclic, aryl, alkoxy, aryloxy, alkyloxy, alkylcarbonyl, alkylcarboxy, amino, and arylthio, which groups can be optionally substituted.

The term "acyl" as used herein refers to a carbonyl substituent, i.e., a C(O)(R) group where R is a straight- or branched-chain saturated aliphatic hydrocarbon group including, without limitation, alkyl, alkenyl, and alkynyl groups. Preferably, the R groups have 1 to about 8 carbon atoms, and more preferably 1 to about 6 carbon atoms. The term "substituted acyl" refers to an acyl group which is substituted with 1 or more groups including halogen, CN, OH, and NO₂.

The term "aryl" as used herein refers to an aromatic system which can include a single ring or multiple aromatic rings fused or linked together where at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl, indene, benzonaphthyl, fluorenyl, and carbazolyl.

The term "substituted aryl" refers to an aryl group which is substituted with one or more substituents including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, and arylthio, which groups can be optionally substituted. Preferably, a substituted aryl group is substituted with 1 to about 4 substituents.

The term "heterocyclic" as used herein refers to a stable 4- to 7-membered monocyclic or multicyclic heterocyclic ring which is saturated, partially unsaturated, or wholly unsaturated. The heterocyclic ring has carbon atoms and one or more heteroatoms including nitrogen, oxygen, and sulfur atoms. Preferably, the heterocyclic ring has about 1 to about 4 heteroatoms in the backbone of the ring. When the heterocyclic ring contains nitrogen or sulfur atoms in the backbone of the ring, the nitrogen or sulfur atoms can be oxidized. The term "heterocyclic" also refers to multicyclic rings in which a heterocyclic ring is fused to an aryl ring. The heterocyclic ring can be attached to the aryl ring through a heteroatom or carbon atom provided the resultant heterocyclic ring structure is chemically stable.

A variety of heterocyclic groups are known in the art and include, without limitation, oxygen-containing rings, nitrogen-containing rings, sulfur-containing rings, mixed heteroatom-containing rings, fused heteroatom containing rings, and combinations thereof. Oxygen-containing rings include, but are not limited to, furyl, tetrahydrofuryl, pyranyl, pyronyl, and dioxinyl rings. Nitrogen-containing rings include, without limitation, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, piperidinyl, 2-oxopiperidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, azepinyl, triazinyl, pyrrolidinyl, and azepinyl rings. Sulfur-containing rings include, without limitation, thienyl and dithiolyl rings. Mixed heteroatom containing rings

include, but are not limited to, oxathieryl, oxazolyl, thiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathieryl, oxazinyl, oxathiazinyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, oxepinyl, thiepinyl, and diazepinyl rings. Fused heteroatom-containing rings include, but are not limited to, benzofuranyl, thionaphthene, indolyl, benazazolyl, purindinyl, pyranopyrrolyl, isoindazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzopyranyl, quinolinyl, isoquinolinyl, benzodiazonyl, naphthylridinyl, benzothienyl, pyridopyridinyl, benzoxazinyl, xanthenyl, acridinyl, and purinyl rings.

The term "substituted heterocyclic" as used herein refers to a heterocyclic group having one or more substituent including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, and arylthio, which groups can be optionally substituted. Preferably, a substituted heterocyclic group is substituted with 1 to 4 substituents.

The term "aroyl" as used herein refers to a carbonyl substituent bound to a phenyl or heterocyclic group. Preferably, the aroyl heterocyclic groups include 2-pyridinyl, 3-pyridinyl, 2-furanyl, 3-furanyl, 3-thiophenyl, 2-pyrimidinyl, and 4-pyrimidinyl groups. The term "substituted aroyl" refers to an aroyl group which is substituted with one or more groups including, without limitation, halogen, CN, OH, and NO₂.

The term "thioalkyl" as used herein is used interchangeably with the term "thioalkoxy", with both referring to an S(alkyl) group, where the point of attachment is through the sulfur-atom and the alkyl group can be optionally substituted.

The term "arylthio" as used herein refers to the S(aryl) group, where the point of attachment is through the sulfur-atom and the aryl group can be optionally substituted.

The term "alkoxy" as used herein refers to the O(alkyl) group, where the point of attachment is through the oxygen-atom and the alkyl group is optionally substituted. The term "aryloxy" as used herein refers to the O(aryl) group, where the

point of attachment is through the oxygen-atom and the aryl group is optionally substituted.

The term "alkylcarbonyl" as used herein refers to the C(O)(alkyl) group, where the point of attachment is through the carbon-atom of the carbonyl moiety and the
5 alkyl group is optionally substituted.

The term "alkylcarboxy" as used herein refers to the C(O)O(alkyl) group, where the point of attachment is through the carbon-atom of the carboxy moiety and the alkyl group is optionally substituted.

The term "aminoalkyl" as used herein refers to both secondary and tertiary
10 amines where the point of attachment is through the nitrogen-atom and the alkyl groups are optionally substituted. The alkyl groups can be the same or different.

The term "halogen" as used herein refers to Cl, Br, F, or I groups.

The compounds of the present invention encompass tautomeric forms of the structures provided herein characterized by the bioactivity of the drawn structures.
15 Further, the compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids, bases, alkali metals and alkaline earth metals.

Physiologically acceptable acids include those derived from inorganic and organic acids. A number of inorganic acids are known in the art and include
20 hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, and phosphoric acids, among others. Similarly, a variety of organic acids are known in the art and include, without limitation, formic, acetic, propionic, oxalic, succinic, glycolic, glucuronic, maleic, furoic, fumaric, citric, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, panthenoic, benzenesulfonic,
25 stearic, sulfanilic, alginic, and galacturonic acids, among others.

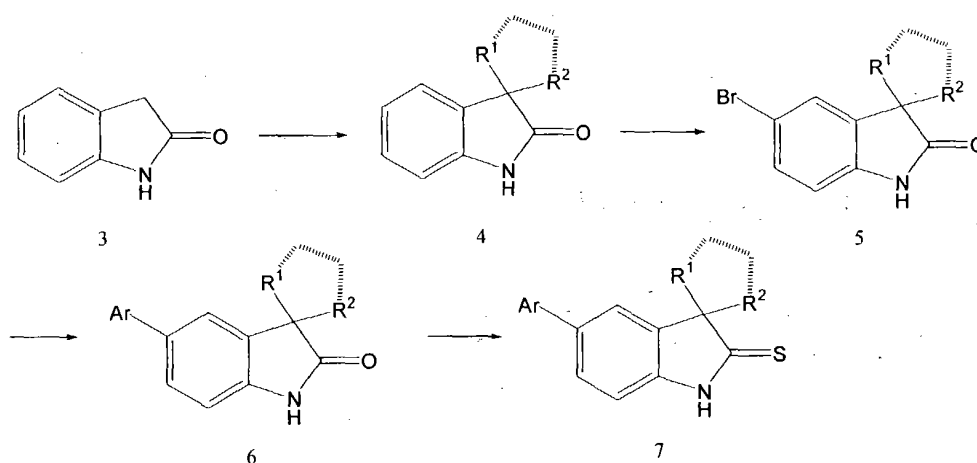
Physiologically acceptable bases include those derived from inorganic and organic bases. A number of inorganic bases are known in the art and include aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc sulfate or phosphate compounds, among others. A number of organic bases are known in the art

and include, without limitation, N,N,-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, and procaine, among others.

Physiologically acceptable alkali salts and alkaline earth metal salts can include, without limitation, sodium, potassium, calcium and magnesium salts in the form of esters, and carbamates. Other conventional "pro-drug" forms can also be utilized which, when delivered in such form, convert to the active moiety *in vivo*.

The compounds of formula I useful in this invention can be prepared following the Schemes illustrated below.

Scheme 1



10

According to Scheme 1, commercially available oxindole 3 can be treated with a strong organometallic base (e.g. butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide) in an inert solvent (e.g. THF, diethyl ether) under nitrogen at reduced temperature (ca. -20 °C) (Kende, et al, Synth. Commun., 12, 1, 1982) in the presence of lithium chloride or N,N,N',N'-tetramethylethylenediamine. The resulting dianion can then be treated with excess electrophile such as an alkyl halide, preferably an iodide. If R₁ and R₂ are to be joined such as the product 4 contains a spirocycle at position 3, then the electrophile should be bifunctional, i.e. a diiodide. Subsequent bromination of 4 proceeds smoothly with bromine in acetic acid (an

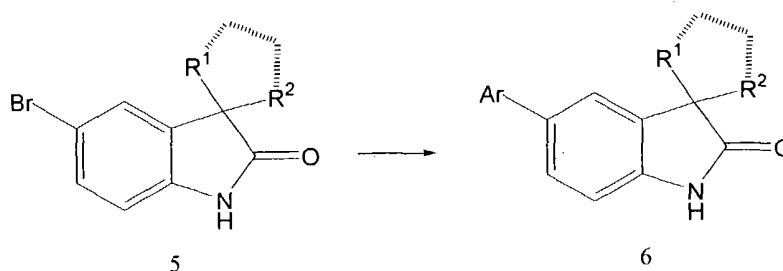
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organic co-solvent such as dichloromethane can be added as required) in the presence of sodium acetate, to afford the aryl bromide 5. The bromide 5 can be reacted with a palladium salt (e.g. tetrakis(triphenylphosphine)palladium(0) or palladium acetate), in a suitable solvent (e.g. THF, dimethoxyethane, acetone, ethanol or toluene) at room temperature under an inert atmosphere (argon, nitrogen). The mixture can then be treated with an aryl or heteroaryl boronic acid or boronic acid ester and a base (sodium carbonate, triethylamine, potassium phosphate) in water or fluoride source (cesium fluoride) under anhydrous conditions. The required product 6 can then be isolated and purified by standard means.

10 Reaction of the indoline-2-one derivative 6 with either Lawesson's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent can provide access to the thiocarbonyl derivative 7. An additive such as sodium hydrogen carbonate can also be useful.

 If R_1 and R_2 are different then the intermediate 4 can be prepared by reacting the dianion of 3 with one equivalent of the electrophile R_1-X (X = leaving group e.g. iodine). The resultant mono-alkylated compound can then be isolated and re-subjected to the reaction conditions using R_2-X , or alternatively used in-situ for the second alkylation with R_2-X . Alternatively if the desired product 7 is to contain $R_2 = H$, then the isolated mono-alkylated intermediate can be taken through the subsequent steps.

Scheme 2

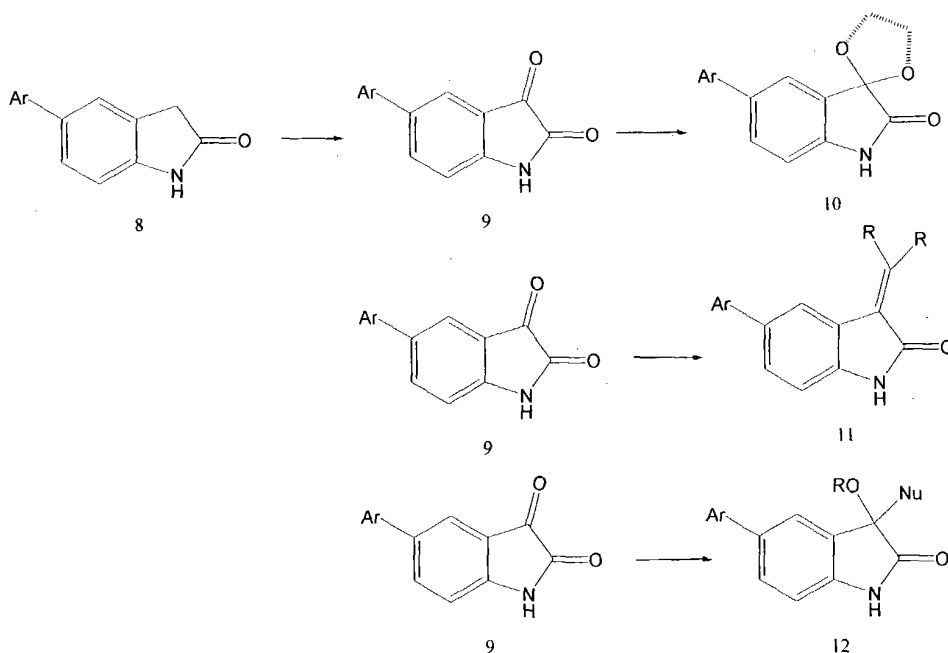


Other methodologies are also available for coupling the pendant aryl or heteroaryl group, Ar, to the oxindole platform, for example reaction of compound 5 with an aryl or heteroaryl stannane, aryl or heteroaryl zinc, or aryl or heteroaryl magnesium halide in the presence of a palladium or nickel catalyst (Scheme 2). The required aryl or heteroaryl-metallic species described above are formed through standard techniques.

Other functionalities can also be installed into the 3-position of the indoline platform according to Scheme 3. Oxidation of the unsubstituted indoline 8, preferably under neutral or acidic conditions (e.g. selenium dioxide in dry dioxane at reflux) can afford the isatin 9. Compound 9 can be further functionalized to provide a ketal 11 by treatment with an alcohol and acid catalyst under dehydrating conditions.

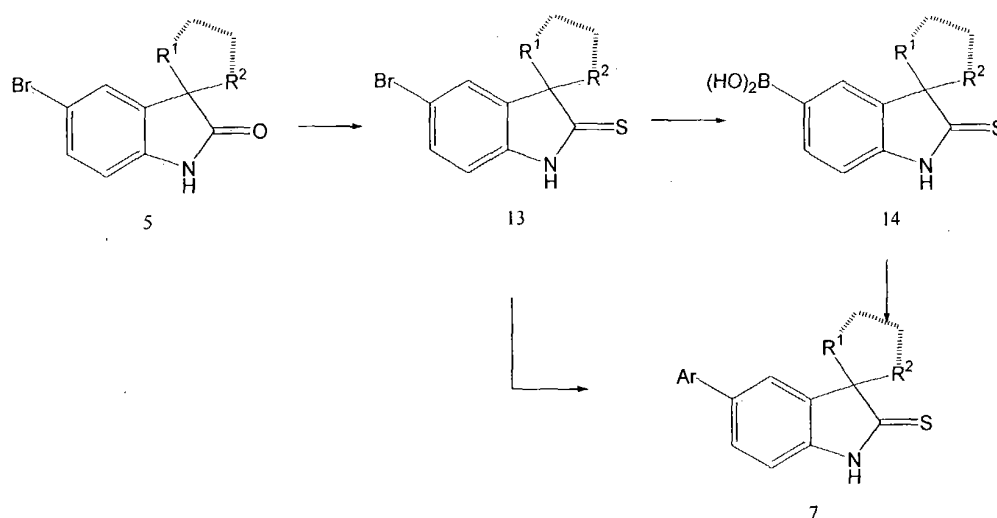
Alternatively reaction of 9 with a second ketone under suitable conditions (piperidine in toluene at reflux; or TiCl_4/Zn in THF at reflux) can afford alkylidene derivatives 11. Reaction of the isatin 9 with a Grignard reagent or organolithium affords tertiary alcohols 12 ($\text{R} = \text{H}$). These alcohols can then be further functionalized by alkylation or acylation procedures.

Scheme 3



Reaction of the indoline-2-one derivative 6 with either Lawesson's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent provides access to the thiocarbonyl derivative 7. An additive such as sodium hydrogen carbonate can also be useful.

Scheme 4

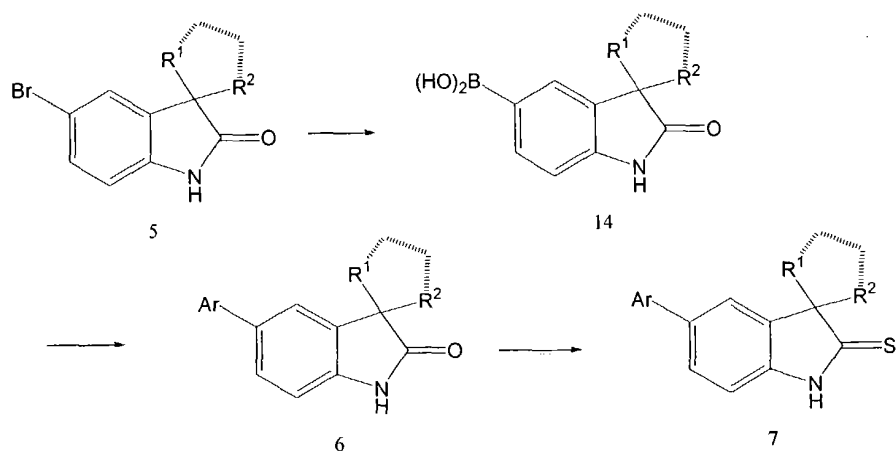


An alternative mode of preparation is to react compound 5 with either Lawesson's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent, under an inert atmosphere (nitrogen or argon) providing access to the thiocarbonyl derivative 13. The reaction of bromide 13 in an anhydrous solvent (e.g. THF, Et₂O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N,N'-tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 14 (Scheme 4). Compound 14 can then be reacted under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base (NaHCO₃,

Na₂CO₃, K₂CO₃, triethylamine, CsF) solvent (toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compounds 7.

5 Alternatively reaction of compound 13 under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base (NaHCO₃, Na₂CO₃, K₂CO₃, triethylamine, CsF) solvent (acetone/water, toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compound 7.

Scheme 5



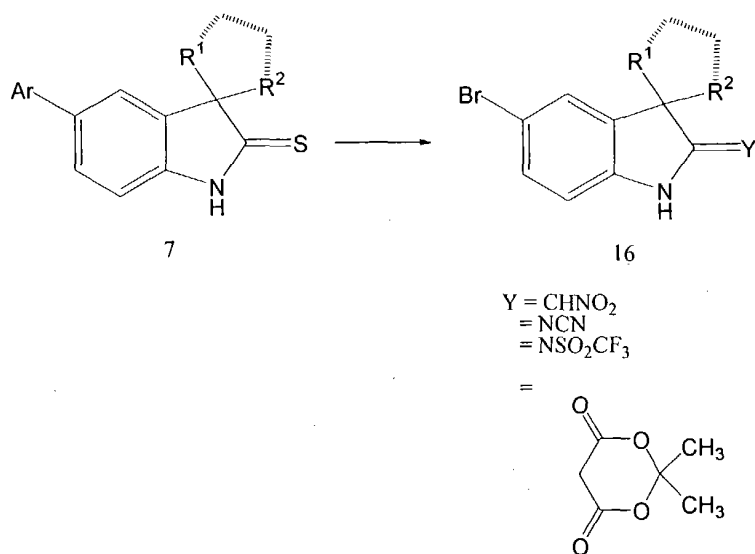
15 Treatment of the bromide 5 in an anhydrous solvent (e.g. THF, Et₂O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N,N'-tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 15 (Scheme 5). Compound 15 can then be reacted under
20 palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0), base (NaHCO₃, Na₂CO₃, K₂CO₃, triethylamine, CsF) solvent (toluene/EtOH/water,

THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compounds 6.

5 An alternative strategy can be to prepare an organozinc or magnesium reagent from compound 5 and react it in-situ with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, under palladium catalyzed conditions to afford compound 6. Such an organo zinc or magnesium species could be prepared by treatment of the bromide 7 in an anhydrous solvent (e.g. THF, Et₂O) with a strong base (sodium hydride preferred,
10 sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N',N'-tetramethylethylenediamine followed after a suitable period of time by reaction with anhydrous zinc chloride or magnesium bromide.

Reaction of the indoline-2-one derivative 6 with either Lawesson's reagent or
15 phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent, under an inert atmosphere (nitrogen or argon) provides access to the thiocarbonyl derivative 15. An additive such as sodium hydrogen carbonate can also be useful.

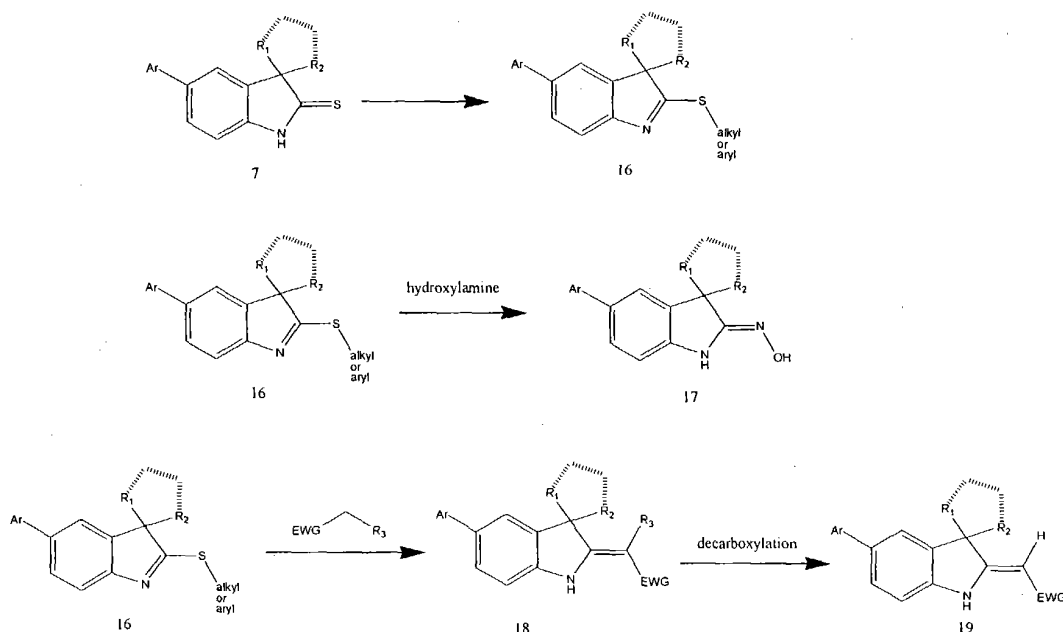
Scheme 6



According to Scheme 6, thioamide derivative 7 can be converted into enamine derivative 16 (Wrobel, et al, J. Med. Chem., 1989, 2493).

Thus, reaction of thioamide 7 (Pg = H, 2-(trimethylsilyl)-ethoxymethyl, benzyl, etc) with triethyloxonium tetrafluoroborate followed by reaction with a nucleophile (nitromethane, cyanamide, trifluoromethanesulfonamide, Meldrum's acid, etc.) followed by removal of the protecting group under appropriate conditions (e.g. tetrabutylammonium fluoride in THF for Pg = 2-(trimethylsilyl)-ethoxymethyl) gives the enamine derivatives 16. Appropriate solvents for the two steps are selected from dichloromethane, THF, dioxane, 1,2-dichloroethane, and the reaction can conducted at a temperature from -78 °C to the boiling point of the solvent under an inert atmosphere (nitrogen or argon).

Scheme 7

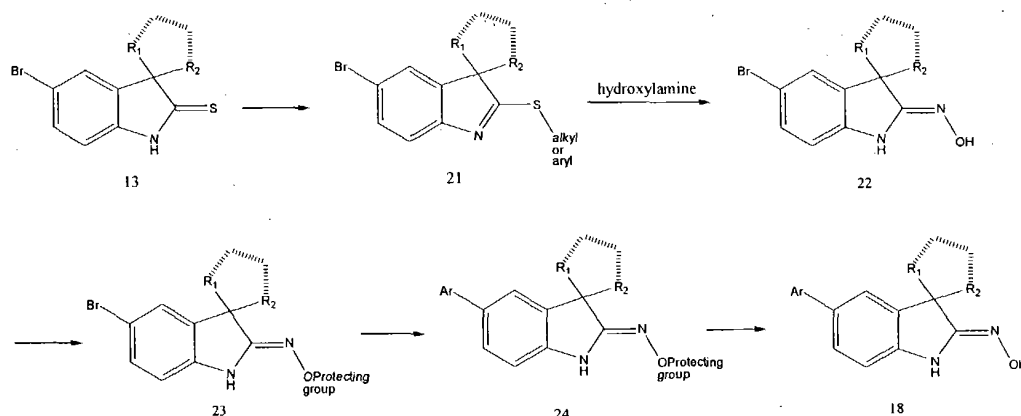


- According to Scheme 7, treatment of intermediate 7 with an alkylating agent, e.g., methyl iodide, ethyl iodide, 2,4-dinitrofluoro benzene, or 4-nitro fluorobenzene, in the presence of a suitable base (e.g. an amine base such as pyridine, triethylamine or di-iso-propylethylamine or lithium, sodium, potassium or cesium carbonate) in a suitable organic solvent (e.g. DMF, THF, DMSO, dioxane or acetonitrile) at a temperature between -78°C and the boiling point of the solvent, can then afford thioimino ether 17. Subsequent reaction of intermediate 17 with hydroxylamine or an acid salt of hydroxylamine (e.g. the hydrochloride) in a suitable solvent (for example, but not limited to, pyridine methanol, ethanol, iso-propanol, DMF, THF or DMSO and optionally in the presence of an additive such as a tertiary amine base or sodium or potassium acetate) at a temperature between -78°C and the boiling point of the solvent can then afford the N-hydroxyamidine 18.
- Similarly treatment of intermediate 17 with a carbon nucleophile such as a malonate derivative (e.g., malononitrile, a cyano acetate ester, a nitro acetate ester or a malonate) in the presence of a suitable base (e.g. an amine base such as pyridine, triethylamine or di-iso-propylethylamine or lithium, sodium, potassium or cesium

carbonate) or a Lewis acid (e.g. boron trifluoride etherate, a lead II salt, titanium tetrachloride, a magnesium II salt, or a silver salt) in a solvent compatible with the chosen base or Lewis acid (e.g. DMF, THF, DMSO, dioxane or acetonitrile, chloroform, benzene, toluene or dichloromethane) can then afford the adduct 19. If
5 the R³ group in adduct 19 is an ester of a carboxylic acid, then it can be decarboxylated directly to give the enamine derivative 20 by treatment with, e.g. sodium iodide in DMSO at a temperature between room temperature and the boiling point of the solvent. Alternatively the ester can be first hydrolyzed to the carboxylic acid by treatment with an aqueous base (e.g. lithium, sodium, or potassium hydroxide)
10 in a suitable solvent (e.g. THF, dioxane, acetonitrile, methanol or ethanol), followed by decarboxylation in the presence of an acid (e.g. hydrochloric or sulfuric acid) in a suitable solvent (e.g. acetonitrile, THF, dioxane) to afford the derivative 20.

Alternatively the xanthate ester of the carboxylic acid can be prepared by reaction with a base such as sodium or potassium hydride in THF, followed by
15 treatment with carbon disulfide. Subsequent reaction with tributyl tin hydride at elevated temperatures in a solvent such as benzene or toluene under an inert nitrogen or argon atmosphere in the presence of a radical initiator such as benzoyl peroxide or azo-bis-iso-butyronitrile would then give the product 20.

Scheme 8



An alternative strategy for synthesizing the product 18 is illustrated by Scheme

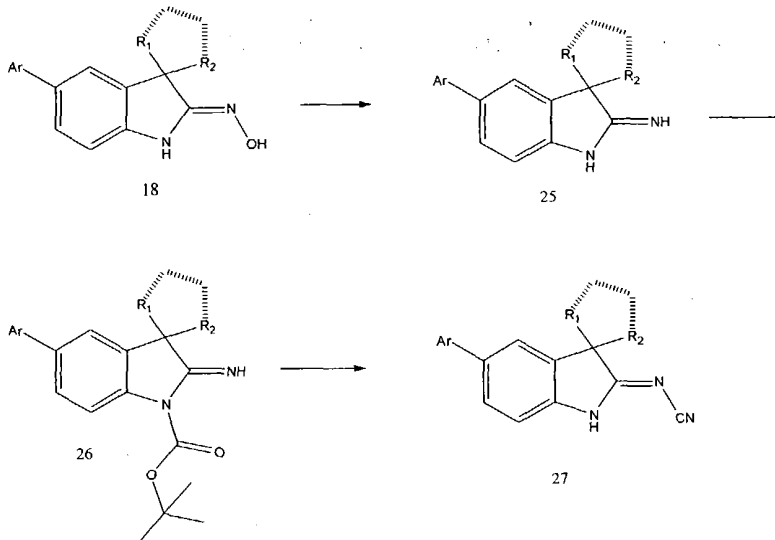
8. The bromide 13 (the corresponding chloride, iodide or triflate ester can also be employed) can be treated with an alkylating agent, e.g., methyl iodide, ethyl iodide, 2,4-dinitrofluoro benzene, or 4-nitro fluorobenzene, in the presence of a suitable base
5 (e.g. an amine base such as pyridine, triethylamine or di-iso-propylethylamine or lithium, sodium, potassium or cesium carbonate) in a suitable organic solvent (e.g. DMF, THF, DMSO, dioxane or acetonitrile) at a temperature between -78°C and the boiling point of the solvent, to afford thioimino ethers 21. Subsequent reaction of intermediate 21 with hydroxylamine or an acid salt of hydroxylamine (e.g. the
10 hydrochloride, hydrobromide) in a suitable solvent (for example but not limited to pyridine methanol, ethanol, iso-propanol, DMF, THF or DMSO and optionally in the presence of an additive such as a tertiary amine base or sodium or potassium acetate) at a temperature between -78°C and the boiling point of the solvent, would then afford the N-hydroxyamidine 22. Intermediate 22 could then be protected with a
15 compatible group (e.g. benzyl ether, acyl derivative, tetrahydropyranyl ether, methoxy methyl ether, silyl ether) to give the derivative 23. Alternately, compound 21 can be reacted directly with a protected hydroxylamine derivative (chosen, but not limited to, from the protecting groups described above) to directly afford derivative 23. Compound 23 can then be reacted with a palladium salt (e.g.
20 tetrakis(triphenylphosphine)palladium(0) or palladium acetate), in a suitable solvent (e.g. THF, dimethoxyethane, acetone, ethanol or toluene) at room temperature under an inert atmosphere (argon, nitrogen). The mixture can then treated with an aryl or heteroaryl boronic acid or boronic acid ester and a base (sodium carbonate, triethylamine, potassium phosphate) in water or fluoride source (cesium fluoride)
25 under anhydrous conditions, and the reaction can then be heated to the boiling point of the solvent. The required product 24 is then isolated and purified by standard means.

Compound 24 can then be deprotected under the conditions prescribed by the nature of the protecting group. For example, if the protecting group is a benzyl ether then treatment with boron tribromide or trimethylsilyl iodide in a suitable solvent

(dichloromethane for example) can afford the compound 18. Other methods to remove the benzyl ether can involve hydrogenation (hydrogen gas or other hydrogen source such as cyclohexadiene or ammonium formate) in the presence of a palladium catalyst. Solvents suitable for such a process include methanol, ethanol, THF, ethyl acetate and dioxane, at a temperature between room temperature and the boiling point of the solvent. If the protecting group was an acetal derivative (tetrahydropyranyl or methoxymethyl ethers) then hydrolysis could be effected under acidic conditions (hydrochloric acid, sulfuric acid, p-toluene sulfonic acid or acidic ion exchange resin) in a solvent such as methanol, ethanol, THF dioxane or acetonitrile. If the protecting group was an acyl derivative (acetate, or benzoate for example) then hydrolysis can be effected under acidic conditions as described above or under basic conditions (lithium, sodium or potassium hydroxide) in a solvent such as an alcohol, THF dioxane or acetonitrile at a temperature between room temperature and the boiling point of the solvent. If the protecting group was a silyl ether, then compound 18 can be prepared by hydrolyzing intermediate 24 under the acidic conditions described above or alternately by exposing compound 24 to a fluoride source (e.g., potassium fluoride, cesium fluoride or tetrabutylammonium fluoride) in a solvent such as an alcohol, THF dioxane or acetonitrile at a temperature between room temperature and the boiling point of the solvent. An inert atmosphere of nitrogen or argon can be necessary.

Another method of synthesizing compound 18 can be to convert the protected N-hydroxy amidine 23 into a boronic acid or boronic acid ester (by lithium halogen exchange followed by quench with tri-isopropyl borate, or palladium catalyzed coupling with diboron pinacolate) and then couple this boronic acid or ester derivative with an aryl chloride, bromide, iodide or triflate under a suitable palladium catalysis system as described previously. Subsequent deprotection as described for Scheme 8 can afford the desired compounds 18.

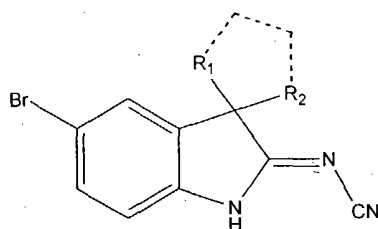
Scheme 9



According to Scheme 9, treatment of the N-hydroxyamidine 18 under reducing conditions (e.g. catalytic hydrogenation, iron in acetic acid or hydrazine-raney nickel) can then afford intermediate 25. Solvents suitable for such a process include methanol, ethanol, THF, ethyl acetate and dioxane, at a temperature between room temperature and the boiling point of the solvent. Protection of the secondary nitrogen (a tertiary butyl carbamate is shown as a non-limiting example) under standard conditions can then give compound 26. Reaction of compound 26 with an electrophilic cyanating agent (e.g. cyanogen bromide, N-cyanobenzotriazole or cyanogen bromide/ 4-dimethylaminopyridine complex) in a suitable solvent (THF acetonitrile or DMF, optionally in the presence of a base such as pyridine or sodium hydride or potassium tert-butoxide) can then afford the desired compound 27. In some cases, the cyanation step can occur with concomitant removal of the secondary nitrogen protecting group, if this deprotection does not occur in-situ then a further hydrolysis step can be required.

An alternate synthesis of compound 27 can follow that of compound 18, Scheme 8, where an N-cyanoamidine bromide 28, prepared from compound 22 adopting a similar strategy to the reactions shown in Scheme 9, can be coupled with a suitable fictionalized aryl boronic acid or boronic acid ester to give compound 27. In

another strategy intermediate 28 can be converted into the corresponding boronic acid or boronic acid ester and coupled in a Suzuki or Suzuki type palladium coupling with a suitable fictionalized aryl bromide.



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II. Formulations of the Invention

The compounds of formula I as described herein can be formulated in any form suitable for the desired route of delivery using a pharmaceutically effective amount of one or more of the compounds of formula I. For example, the compositions of the invention can be delivered by a route such as oral, dermal, transdermal, intrabronchial, intranasal, intravenous, intramuscular, subcutaneous, parenteral, intraperitoneal, intranasal, vaginal, rectal, sublingual, intracranial, epidural, intratracheal, or by sustained release. Preferably, delivery is oral.

A pharmaceutically effective amount of the compound(s) used according to the present invention can vary depending on the specific compound(s), mode of delivery, severity of the skin disorder, and any other active ingredients used in the formulation. The dosing regimen can be adjusted to provide the optimal therapeutic response. Several divided doses can be delivered daily, e.g., in divided doses 2 to 4 times a day, or a single dose can be delivered. The dose can however be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

Preferably, the delivery can be on a daily, weekly, or monthly basis, and more preferably on a daily delivery. Daily dosages can be lowered or raised based on the periodic delivery.

The compound(s) of formula I can be delivered at a daily dosage of from about 0.1 to about 500 mg, more preferably about 0.1 to about 100 mg, and most preferably from about 0.1 to about 50 mg. The compound(s) of formula I can be combined with one or more pharmaceutically acceptable carriers or excipients including, without
5 limitation, solid and liquid carriers which are compatible with the compositions of the present invention. Such carriers can include adjuvants, syrups, elixirs, diluents, binders, lubricants, surfactants, granulating agents, disintegrating agents, emollients, and combinations thereof.

Adjuvants can include, without limitation, flavoring agents, coloring agents,
10 preservatives, and supplemental antioxidants, which can include vitamin E, ascorbic acid, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).

Elixers and/syrups can be prepared from acceptable sweeteners such as sugar, saccharine or a biological sweetener, a flavoring agent, and/or solvent. In one embodiment, a syrup can contain about 10 to about 50% of a sugar carrier. In another
15 embodiment, the elixir can contain about 20 to about 50% of an ethanol carrier.

Diluents can include materials in which the compound can be dispersed, dissolved, or incorporated. Preferably, the diluents include water, lower monovalent alcohols, and low molecular weight glycols and polyols, including propylene glycol, diethylene glycol, polyethylene glycol, polypropylene glycol, glycerol, butylene
20 glycol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, sorbitol esters, butanediol, ether propanol, ethoxylated ethers, propoxylated ethers, oils such as corn, peanut and sesame oils, dimethylsulfoxide (DMSO), dimethylformamide (DMF), and combinations thereof. Preferably, the diluent is water.

25 Binders can include, without limitation, cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethylene glycol, starch, sugars such as sucrose, kaolin, and lactose, among others.

Lubricants can include magnesium stearate, light anhydrous silicic acid, talc and sodium lauryl sulfate, among others.

Granulating agents can include, without limitation, silicon dioxide, microcrystalline cellulose, starch, calcium carbonate, pectin, and crospovidone,
5 polyplasdone, among others.

Disintegrating agents can include starch, carboxymethylcellulose, hydroxypropylstarch, substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate, and calcium citrate, among others

Emollients can include, without limitation, stearyl alcohol, mink oil, cetyl
10 alcohol, oleyl alcohol, isopropyl laurate, polyethylene glycol, olive oil, petroleum jelly, palmitic acid, oleic acid, and myristyl myristate.

III. Therapeutic Regimens

The present invention provides dosing regimens utilizing the compound(s) of
15 formula I with a physiologically acceptable carrier. The compositions of the invention can be delivered by a route such as oral, dermal, transdermal, intrabronchial, intranasal, intravenous, intramuscular, subcutaneous, parenteral, intraperitoneal, intranasal, vaginal, rectal, sublingual, intracranial, epidural, intratracheal, or by sustained release. Preferably, delivery is oral.

20 In one embodiment, the compounds are delivered orally by tablet, capsule, microcapsules, dispersible powder, granule, suspension, syrup, elixir, and aerosol. Desirably, when the compositions are delivered orally, delivery is by tablets and hard- or liquid-filled capsules.

In another embodiment, the compounds are delivered intravenously,
25 intramuscularly, subcutaneously, parenterally and intraperitoneally in the form of sterile injectable solutions, suspensions, dispersions, and powders which are fluid to the extent that easy syringe ability exists. Such injectable compositions are sterile, stable under conditions of manufacture and storage, and free of the contaminating action of microorganisms such as bacteria and fungi.

Injectable formations can be prepared by combining the compound with a liquid. The liquid can be selected from among water, glycerol, ethanol, propylene glycol and polyethylene glycol, oils, and mixtures thereof, and more preferably the liquid carrier is water. In one embodiment, the oil is vegetable oil. Optionally, the liquid carrier contains a suspending agent. In another embodiment, the liquid carrier is an isotonic medium and contains 0.05 to about 5% suspending agent.

In a further embodiment, the compounds are delivered rectally in the form of a conventional suppository.

In another embodiment, the compounds are delivered vaginally in the form of a conventional suppository, cream, gel, ring, or coated intrauterine device (IUD).

In yet another embodiment, the compositions are delivered intranasally or intrabronchially in the form of an aerosol.

In a further embodiment, the compounds are delivered transdermally or by sustained release through the use of a transdermal patch containing the composition and an optional carrier that is inert to the compound, is nontoxic to the skin, and allows for delivery of the compound for systemic absorption into the blood stream. Such a carrier can be a cream, ointment, paste, gel, or occlusive device. The creams and ointments can be viscous liquid or semisolid emulsions. Pastes include absorptive powders dispersed in petroleum or hydrophilic petroleum. Further, a variety of occlusive devices can be utilized to release the active reagents into the blood stream and include semi-permeable membranes covering a reservoir contain the active reagents, or a matrix containing the reactive reagents.

The use of sustained delivery devices can be desirable, in order to avoid the necessity for the patient to take medications on a daily basis. The term "sustained delivery" is used herein to refer to delaying the release of an active agent, i.e., a compound of the invention, until after placement in a delivery environment, followed by a sustained release of the agent at a later time. A number of sustained delivery devices are known in the art and include hydrogels (US Patent Nos. 5,266,325; 4,959,217; 5,292,515), osmotic pumps (US Patent Nos. 4,295,987 and 5,273,752 and

European Patent No. 314,206, among others); hydrophobic membrane materials, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA); bioresorbable polymer systems (International Patent Publication No. WO 98/44964 and US Patent Nos. 5,756,127 and 5,854,388); and other bioresorbable implant devices composed of, 5 for example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers (US Patent No. 5,817,343). For use in such sustained delivery devices, the compounds of the invention can be formulated as described herein. See, US Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

In yet another embodiment, the compounds are topically delivered using a 10 topical vehicle including creams, pastes, gels, ointments, lotions, liquids, solutions, suspensions, or foams or can be alone delivered prior or subsequent to the topical vehicle. Topical compositions can be applied to the area of the body which is afflicted with the skin disorder and includes the face, scalp, legs, arms, torso, or armpits. Preferably, the topical vehicles are anti-comedogenic.

15 Skin conditioning agents can include any reagent which provides a conditioning effect to the skin and/or does not clog the pores of the skin. A number of skin conditioning agents are known in the art and include, without limitation, skin conditioning agents that can be applied to the skin, including water-based lotions, creams, pastes, gels, ointments or foams.

20 The regimens of the invention can include the continuous delivery of the compounds of the invention. In another embodiment, the regimens can include the periodic discontinuation of delivery of the compounds of the invention. Such periodic discontinuation can include delivery of a placebo during the period of time where the compounds of the invention are not delivered to the patient. Alternatively, no placebo 25 or active agent is delivered to the patient when the compounds are not being delivered to the patient.

By the term "placebo" or "inactive agent" is meant a reagent having pharmacological properties that are not relevant to the condition being treated, i.e.,

does not contain an active agent. Typical placebos include sugar as the primary constituent.

By the term "active agent" is meant any reagent which assists in treating a hormone-related condition.

5 The method of the present invention can be carried out over a cycle of 21 or more days, preferably 21 or more consecutive days, more preferably 21, 28, 30, or 31 days, and most preferably 21 or 28 days. One of skill in the art would readily be able to select and adjust the appropriate period of delivery.

10 The terminal portion of a cycle can be the last 1 to about 10 days of the cycle, and preferably the last 7 days of the cycle. In one embodiment, the terminal portion of the 28-day cycle can include the last 7 days of the cycle, i.e., days 22 to 28 of the 28-day cycle. The terminal portion of a cycle can include the delivery of an agent other than the compositions of the invention and is preferably a placebo. Alternatively, no agent or placebo is delivered during the terminal portion of the cycle.

15 The regimen can include delivering a daily dosage of the compound of formula I, which is incorporated into a single daily dosage unit. Delivery of the compounds of formula I can be prior to, simultaneous with, or subsequent to the delivery of other reagents that can be used according to the present invention.

20 The regimen can further include alternating delivery of the compounds of formula I alone, other reagent(s) that can be used according to the present invention, and a combination of the compound and the other reagent(s).

25 In one embodiment, a single daily dosage of the compound of formula I can be delivered for the entire 21-day, 28-day, 30-day, or 31-day cycle. Alternatively, a single daily dosage of the compound of formula I can be delivered for the first 21 days of a 28-day, 30-day, or 31-day cycle. A single daily dosage of the compound of formula I can also be delivered for the first 24 days of a 28-day, 30-day, or 31-day cycle.

 The regimen can further include alternating delivery of the compounds of formula I alone, an estrogen alone, and a combination of the compound and the

estrogen. The regimen can also include the delivery of another reagent prior to, in conjunction with, or subsequent to the compound of formula I and the estrogen.

In one embodiment, a single combined daily dosage of the compound of formula I and an estrogen can be delivered for the entire 21-day, 28-day, 30-day, or 31-day cycle. Alternatively, a single combined daily dosage of the compound of formula I and an estrogen can be delivered for the first 21 days of a 28-day, 30-day, or 31-day cycle. A single combined daily dosage of the compound of formula I and an estrogen can also be delivered for the first 24 days of a 28-day, 30-day, or 31-day cycle.

In a further embodiment, a daily dosage of the compound of formula I can be delivered by one route of delivery and a daily dosage of an estrogen can be delivered by a second route of delivery for the entire 21-day, 28-day, 30-day, or 31-day cycle. Alternatively, a daily dosage of the compound of formula I can be delivered by one route of delivery and a daily dosage of an estrogen can be delivered by a second route of delivery for the first 21 days of a 28-day, 30-day, or 31-day cycle. Further, a daily dosage of the compound of formula I can be delivered by one route of delivery and a daily dosage of an estrogen can be delivered by a second route of delivery for the first 24 days of a 28-day, 30-day, or 31-day cycle.

In another embodiment, a daily dose of the compound of formula I can be delivered, followed by a daily dose of an estrogen for the entire 21-day, 28-day, 30-day, or 31-day cycle. Alternatively, a daily dose of the compound of formula I can be delivered, followed by a daily dose of an estrogen for the first 21 days of a 28-day, 30-day, or 31-day cycle. Alternatively, a daily dosage of the compound of formula I can be delivered, followed by a daily dosage of an estrogen for the first 24 days of a 28-day, 30-day, or 31-day cycle.

In a further embodiment, the compounds of formula I are delivered with an estrogen for the first 14 to 24 days of a 28-day cycle, followed by delivery of the estrogen alone for a period of 1 to 11 days beginning on any cycle day between day 14 and 24.

In another embodiment, the compounds of formula I can be delivered for the initial 18 to 21 days of a 28-day cycle, followed by delivery of an estrogen alone for from 1 to 7 days.

In yet a further embodiment, the compounds of formula I can be delivered
5 alone over a 28 day cycle for the first 21 days, followed by delivery of an estrogen alone from day 22 to day 24.

The dosage regimens can be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component can be delivered daily or the dose can be proportionally increased or reduced as indicated by the
10 exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit can also include divided units which are delivered over the course of each day of the cycle contemplated.

Optionally, other conventional acne-reducing compounds are included in the compositions and/or regimens of the invention. Such acne-reducing compounds can
15 assist in the reduction of redness and/or blemishes. A large number of acne-reducing compounds are known in the art and include carotenoid agents, vitamin B sources, zinc compounds, and combinations thereof. See, US Patent No. 5,962,517.

Carotenoid agents can be included in the composition of the invention or can be alone delivered prior or subsequent to the compound or composition and include
20 those carotenoids which exhibit antioxidant behavior. Preferably, the carotenoid agent includes beta-carotene, canthaxanthin, zeaxanthin, lycopene, lutein, crocetin, capsanthin, and vitamin A sources. The vitamin A sources can include vitamin A acetate or vitamin A palmitate. More preferably, the carotenoid agent is beta-carotene.

25 Vitamin B sources can also included in the composition of the invention or can be alone delivered prior or subsequent to the composition to assist or promote the formation of amino acids and collagen. Preferably, the vitamin B source is a B₆ source, which can include, without limitation, pyridoxine, pyridoxal, and pyridoxamine, and more preferably is pyridoxine.

Further, zinc compounds can be included in the composition of the present invention or can be alone delivered prior or subsequent to the composition. The zinc compound can include any zinc compound, preferably a zinc compound which promotes the reduction of inflammation, more preferably zinc ascorbic acid or zinc
5 ascorbate, and most preferably zinc ascorbate.

Penetration enhancers, when used according to the method of the invention in treating hirsutism, can include any reagent that enhances the penetration of a compound through one or more layers of the skin and/or to the site of the skin disorder. A number of penetration enhancers are known in the art and include, but are
10 not limited to, urea, proan-2-ol, polyoxyethylene ethers, terpenes, cis-fatty acids, including oleic acid and palmitoleic acid, acetone, laurocapram dimethyl sulfoxide, 2-pyrrolidone, oleyl alcohol, glyceryl-3-stearate, cholesterol, myristic acid isopropyl ester, propylene glycol, and combinations thereof.

When included in the compositions of the present invention, the estrogens can
15 include natural estrogens, synthetic estrogens, catechol estrogens, conjugated estrogens, and non-steroidal estrogens, among others, or pharmaceutically acceptable salts or esters thereof. In one embodiment, the estrogen is a natural estrogen including estrone, including the acetate, propionate, sulfate, and sulfate piperazine ester salts; estradiol, including the 3-benzoate, 17b-cypionate, 17-propionate, d-propionate,
20 hemisuccinate, 17-heptanotate, 17-undecanoate, and 17-valerate ester salts; or estriol. In another embodiment, the estrogen is a synthetic estrogen including ethinyl estradiol. In a further embodiment, the estrogen is a conjugated estrogen including conjugated equine estrogens and sodium estrone sulfate and is available in formulations for intravenous, intramuscular, and topical administration (Wyeth). In a
25 further embodiment, the estrogen is a catechol estrogen including 2- or 4-hydroxyestrogens. In yet another embodiment, the nonsteroidal estrogen is diethylstilbestrol. See, Chapter 50 entitled "Hormones" in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, Easton, Pennsylvania, 1990. The desired estrogen may however be selected from a variety of products

commercially available. One of skill in the art would readily be able to select the estrogen, as well as dosage, that achieves the desired effect. Preferably, the estrogen is present in the formulation at about 0.01 mg to about 1.0 mg.

Other reagents can be delivered in combination with the compositions of the present invention. Alternatively, such reagents can be alone administered prior or subsequent to the compositions of the invention. Such reagents can include drying agents including alcohols and benzoyl peroxides; vitamin C and D sources; amino acid reagents; enzyme activators; mineral oil; lanolin; propylene glycol; sodium lauryl sulfate; among others, and combinations thereof. Further, oral reagents include antibiotics; anti-inflammatory agents; herbal extracts including burdock root, yellow dock, horsetail, dandelion root, licorice root, echinacea, kelp, cayenne, sassafras, and elder flowers; xanthan gum; cytokines, androgens, and antiprogestins. Antibiotics, can also be applied as in a topical vehicle.

In addition, the compositions of the invention can be delivered in conjunction with other skin treatments, including laser surgery.

The term "enzyme activator" is meant to describe a reagent which activates fat and glucose metabolism and thereby results in the prevention of future acne occurrences. Preferably, the enzyme activator is a transition metal complex, more preferably is a group 5 or 6 transition metal complex, and most preferably a vanadium or chromium complex.

IV. Pharmaceutical Kits

The present invention provides kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral delivery over 21-day, 28-day, 30-day, or 31-day cycles, among others, and more preferably for one oral delivery per day. When the compositions are to be delivered continuously, a package or kit can include the composition in each tablet. When the compositions are to be delivered with periodic

discontinuation, a package or kit can include placebos on those days when the composition is not delivered.

The kits are also preferably organized to indicate a single oral formulation or combination of oral formulations to be taken on each day of the cycle, preferably
5 including oral tablets to be taken on each of the days specified, and more preferably one oral tablet will contain each of the combined daily dosages indicated.

In one embodiment, a kit can include a single phase of a daily dosage of the compound of formula I over a 21-day, 28-day, 30-day, or 31-day cycle. Alternatively, a kit can include a single phase of a daily dosage of the compound of formula I over
10 the first 21 days of a 28-day, 30-day, or 31-day cycle. A kit can also include a single phase of a daily dosage of the compound of formula I over the first 28 days of a 30-day or 31-day cycle.

In a further embodiment, a kit can include a single combined phase of a daily dosage of the compound of formula I and an estrogen over a 21-day, 28-day, 30-day,
15 or 31-day cycle. Alternatively, a kit can include a single combined phase of a daily dosage of the compound of formula I and an estrogen over the first 21 days of a 28-day, 30-day, or 31-day cycle. A kit can also include a single combined phase of a daily dosage of the compound of formula I and an estrogen over the first 28 days of a 30-day or 31-day cycle.

20 In another embodiment, a 28-day kit can include a first phase of from 14 to 28 daily dosage units of the compound of formula I; a second phase of from 1 to 11 daily dosage units of an estrogen; and, optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle.

In yet a further embodiment, a 28-day kit can include a first phase of from 14
25 to 21 daily dosage units of the compound of formula I; a second phase of from 1 to 11 daily dosage units of an estrogen; and, optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle.

In another embodiment, a 28-day kit can include a first phase of from 18 to 21 daily dosage units of a compound of formula I; a second phase of from 1 to 7 daily

dose units of an estrogen; and, optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0 to 9 days in the 28-day cycle.

In a preferred embodiment, a 28-day kit can include a first phase of 21 daily dosage units of a compound of formula I; a second phase of 3 daily dosage units for
5 days 22 to 24 of an estrogen; and, optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Preferably, the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is delivered. It is further preferable that the daily dose units described are to be delivered in the order
10 described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle.

A number of packages or kits are known in the art for the use in dispensing pharmaceutical agents for oral use. Preferably, the package has indicators for each
15 day of the 28-day cycle, and more preferably is a labeled blister package, dial dispenser package, or bottle.

The following examples are provided to illustrate the invention and do not limit the scope thereof. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, modifications can be
20 made which are meant to be encompassed by the spirit and scope of the invention.

EXAMPLES

Example 1 – Treatment of Acne

25 A twenty-five year old human patient having acne vulgaris is treated according to the present invention. Specifically, 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide is orally delivered to the patient daily. Delivery is in the form of a tablet formulated to contain about 20 mg of

5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide.

Forty-five to sixty days after the treatment, a decrease in the presence of lesions caused by acne vulgaris is noticed. After about 24 weeks, improvement in the
5 acne vulgaris is observed.

Example 2 – Treatment of hirsutism

Male intact golden Syrian hamsters, which display oval shaped flank organs, one on each side, are utilized to demonstrate hair growth. The flank organs are
10 depilated and/or shaved to remove the initial presence of hair. To one organ is applied a cream containing 5 mg 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide. After about thirteen applications, one application per day for five days a week, the flank organs are shaved and the amount of recovered hair from each organ is determined.

15 From these data, it is determined that the compositions of the invention provide a reduction in hair growth of at least about 15%.

Example 3 – Conditioning the Skin

A thirty year old human patient having a severe form of eczema is treated
20 according to the present invention. Specifically, about 50 mg of 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide is delivered to the patient daily.

Thirty days after the treatment, a decrease in the dryness affected to the skin is noticed. After about 12 weeks, improvement in the eczema is observed.

25 From these data, it is determined that the compositions of the invention are effective in conditioning the skin.

Example 4 – Anti-androgenic Effect

The androgen receptor (AR) agonistic and antagonistic activity of the compositions of the invention in the L929 cells which express the AR but not the PR was evaluated as described in Zhang et al., Steroids, 65(10-11): 637-643 (October-November 2000).

Cells were plated in 96-well plates at 25,000 cells/well in DMEM (BioWhittaker) with 10% (v/v) fetal bovine serum (FBS). The next day, cells were infected with the adenovirus PRE-tk-luciferase reporter construct (2×10^9 pfu/ml particles) and kept in DMEM containing 10% charcoal stripped FBS for an additional 24 hours. Cells were then separately treated with a range of concentrations of the dihydrotestosterone (DHT) reference, the 2-hydroxyflutamide (2-OH-fluta) reference, or 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide diluted in the same medium. To test the anti-androgenic activity, cells were co-treated with 3 nM DHT. Luciferase activity was measured 24 hours following the treatment. The following data were obtained:

Table 1

Compound	IC50 (nM)
5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide	313
2-OH-fluta	49.9

From these data, it was noted that 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide showed significant antagonistic activity over a nine point dose response and only marginal agonistic activity at the maximum concentration tested (i.e., 10 nM).

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.